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| 09/912,947 | 07/25/2001 | Bjorn Dahlback | INL-036DV | 7730 |

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| EXAMINER | |
|---|---|
| SWITZER, JULIET CAROLINE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

DATE MAILED: 06/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/912,947 | DAHLBACK, BJORN | |
| | Examiner | Art Unit | |
| | Juliet C. Switzer | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *40-42 and 44-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-42 and 44-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/9/04 has been entered.

2. The examiner in this application has changed. All previous prosecution history including previously filed IDS have been considered. Please address future correspondence to Examiner Juliet Switzer, Art Unit 1634.

3. Claims 40-42 and 44-61 are pending and examined herein.

### *Priority*

4. The claim to priority is not clear. The application data sheet filed 7/25/01 lists a claim to priority to 08/500917, indicating that the 08 application was filed 1/28/94. However, the 08 application is a 371 of PCT/SE94/00070, which was filed 1/28/94. The 08 application itself has a later filing date of 10/20/95. A supplemental ADS should submitted which indicates the actual US filing date of the 08 application and that the 08 application is a 371 of PCT/SE94/00070, which was filed 1/28/94. Further, it is recommended that the supplemental ADS recite the foreign priority information, in the interest of having all of the priority information listed in a single location in the application file.

### *Information Disclosure Statement*

5. The signed copy of the 1449 filed 1/22/02 that was previously mailed to applicant was not signed at the bottom of each sheet. Enclosed with this office action is a signed copy of the 1449 with a signature at the bottom of the sheet.

### *Specification*

6. The substitute specification filed 3/6/02 has been entered. Paragraph numbers in this office action refer to the numbering in the specification filed 3/6/02.

7. The specification is objected to because the description of the drawings because it does not contain a reference to both figures 4A and 4B. The description only discusses Figure 4 (¶ 0016). Correction is required.

### *Oath/Declaration*

8. The oath filed 2/11/04 has been entered into the application.

### *Claim Rejections - 35 USC § 112, 2nd ¶*

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 40-42, 44-45, 46, and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 is indefinite because the preamble sets forth a method for determining if an individual has an increased risk of developing thrombosis due to inherited APC-resistance, yet the final process step recites only detecting a gene mutation that gives rise to the expression of a mutated factor V/Va molecule. The claim does not set forth the relationship between the

determining recited in the preamble and the detecting of the method step, and therefore, it is not clear if the method is meant to actually determine a predisposition or if it meant only to encompass detecting the presence of a mutation. Claims 41-42 and 44-45 are indefinite for the same recitation.

Claim 46 is indefinite because the preamble sets forth a method for determining if an individual has an increased risk of developing, yet the single process step in the claim recites only comparing the individual's Factor V gene sequence to a normal Factor V gene sequence. The claim does not set forth the relationship between the determining recited in the preamble and the comparing step, and therefore, it is not clear if the method is meant to actually determine a predisposition or if it meant only to encompass comparing two gene sequences. Claim 53 is indefinite for the same recitation. Further, in claim 53, the phrase "the factor V gene" lacks proper antecedent basis in the claim as the claim previously recites two different Factor V genes, the individual's and a "normal" Factor V gene sequence.

***Claim Rejections - 35 USC § 112, 1st ¶***

11. Claims 40-42 and 44-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature of the Invention**

The invention is drawn to methods for predicting an increased risk of developing thrombosis and/or APC resistance caused by a gene mutation via screening of samples for the occurrence of Factor V gene mutations that give rise to the expression of a mutated Factor V/Va

molecule. Thus, the nature of the invention requires the knowledge of a mutation in the Factor V gene which is associated with an increased risk of developing thrombosis and/or APC resistance caused.

**Breadth of the Claims**

Claim 40 is drawn to a method for determining if an individual has an increased risk of developing thrombosis due to inherited APC-resistance caused by a gene mutation, and comprises a step of detecting the occurrence of a Factor V gene mutation. Claims 40-42 and 44-45 depend from claim 40, and further define the mutation. None of the claims actually give the structure of a mutation within the Factor V gene.

Claim 46 is drawn to a method for determining an increased risk of developing thrombosis and contains a single method step of comparing the individual's Factor V gene sequence to a normal Factor V gene sequence. The implication of the claim is that the determination of risk is based on an abnormality of the patient's gene sequence, though the claim does not give the structure of the abnormality. Claim 53 depends from claim 46 and requires the genes are compared via sequencing.

Claim 47 is drawn to a method for determining an increased risk of developing thrombosis and comprises a step of determining the presence of at least one Factor V gene mutation in the individual, wherein the presence of the gene mutation is indicative of an increased risk of thrombosis. Claims 49-52 depend from claim 47 and further define the determining steps.

Claim 48 is drawn to a method fro determining an increased risk of APC-resistance and comprises a step of determining the presence of at least one Factor V gene mutation in the

individual, wherein the presence of the gene mutation is indicative of an increased risk of thrombosis. Claims 49-52 depend from claim 48 and further define the determining steps.

Claim 54 is drawn to a method for identifying an occurrence of a Factor V gene mutation associated with APC-resistance comprising determining an occurrence of the mutation in the Factor V gene locus. Claims 55-61 depend from claim 54.

Thus, the claims encompass screening methods which detect any mutation within the Factor V gene, with some claims requiring that the mutation give rise to the expression of a mutated Factor V/Va molecule.

**Teachings of the Specification, Working examples**

The specification teaches at ¶ 0081 that a "neutral polymorphism" in the Factor V gene has linkage with inherited APC resistance. The specification does not give the structure of the polymorphism, i.e. wherein within the gene the polymorphism is located or what base change occurs, nor does the specification disclose any polymorphism or mutation within the Factor V gene that result in the expression of a mutated factor V/Va molecule.

There are no working examples in the specification which exemplify an embodiment of the claimed methods.

**State of the Prior Art**

The prior art does not provide any genetic variations within the Factor V gene that are associated with thrombosis or APC resistance.

**Level of Unpredictability**

There is a large body of knowledge in the art related to polymorphisms in general, and their association with diseases or disease states. Even in cases where an association between a

particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). In some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The instant application does not teach any mutations or polymorphisms within the human Factor V gene. There is a disclosure that a single "neutral polymorphism" is known to exist, but there is not disclosure of the polymorphisms itself such that it could be used in an assay to predict the presence of the phenotype. It is highly unpredictable which nucleotides within the human Factor V gene are the polymorphic or mutated nucleotides that are associated with disease.

**Quantity of Experimentation**

The quantity of experimentation necessary to practice the claimed invention is quite high, and would involve the screening and analysis of the Factor V gene from hundreds of patients to

identify any putative polymorphisms and mutations within the gene and to establish a relationship between these and the recited phenotypes.

**Conclusion**

Considering all of these factors, it is concluded that it would require undue experimentation to practice the claimed invention.

12. Claims 40-42 and 44-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is reiterated from the previous office action and applied to the newly added and/or amended claims.

Claim 40 is drawn to a method for determining if an individual has an increased risk of developing thrombosis due to inherited APC-resistance caused by a gene mutation, and comprises a step of detecting the occurrence of a Factor V gene mutation. Claims 40-42 and 44-45 depend from claim 40, and further define the mutation. None of the claims actually give the structure of a mutation within the Factor V gene.

Claim 46 is drawn to a method for determining an increased risk of developing thrombosis and contains a single method step of comparing the individual's Factor V gene sequence to a normal Factor V gene sequence. The implication of the claim is that the determination of risk is based on an abnormality of the patient's gene sequence, though the claim

does not give the structure of the abnormality. Claim 53 depends from claim 46 and requires the genes are compared via sequencing.

Claim 47 is drawn to a method for determining an increased risk of developing thrombosis and comprises a step of determining the presence of at least one Factor V gene mutation in the individual, wherein the presence of the gene mutation is indicative of an increased risk of thrombosis. Claims 49-52 depend from claim 47 and further define the determining steps.

Claim 48 is drawn to a method fro determining an increased risk of APC-resistance and comprises a step of determining the presence of at least one Factor V gene mutation in the individual, wherein the presence of the gene mutation is indicative of an increased risk of thrombosis. Claims 49-52 depend from claim 48 and further define the determining steps.

Claim 54 is drawn to a method for identifying an occurrence of a Factor V gene mutation associated with APC-resistance comprising determining an occurrence of the mutation in the Factor V gene locus. Claims 55-61 depend from claim 54.

The specification teaches at ¶ 0081 that a "neutral polymorphism" in the Factor V gene has linkage with inherited APC resistance. The specification does not give the structure of the polymorphism, i.e. wherein within the gene the polymorphism is located or what base change occurs, nor does the specification disclose any polymorphism or mutation within the Factor V gene that result in the expression of a mutated factor V/Va molecule. The knowledge of such a variation within the Factor V gene that is linked to thrombosis and/or APC resistance is essential for the practice of the claimed invention, as each of the claimed methods is directed towards assaying for such a molecule as an indicator of the particularly recited phenotype. Absent a

disclosure of such a mutation/polymorphisms/variation, the claimed methods lacks proper written description.

**Response to Remarks**

Applicant's response summarizes relevant case law at pages 5-6.

Applicant argues beginning at the bottom of page 6 that unlike Fiers and Eli Lilly, which claimed nucleic acid compositions, the instant application claims methods, and that the claimed methods need not describe an unclaimed mutation in the Factor V gene. This is not persuasive. The practice of the claimed methods requires the identification of mutations within and linked to the Factor V gene which are not described, indeed which the specification does not provide any description of beyond suggesting that they might exist. While applicant is not claiming nucleic acids comprising these mutations, they are essential for the practice of the claimed methods. Though the cited case law is directed towards a discussion of products in particular, the guidance of the court is appropriately applied to these claims which rely on the detection of nucleic acid sequences for which no written description is provided in the specification.

Applicant further argues that there is a clear correlation between APC-resistance and Factor V gene described throughout the specification, citing in particular page 20 of the specification, which teaches that there is a strong linkage between a known polymorphism in the Factor V gene and expression of APC-resistance. It appears that this is the only portion of the specification that particularly addresses the Factor V gene in particular, with the rest of the specification focusing on the Factor V protein activity. This portion of the specification (p. 18 of the replacement spec, ¶0081) teaches that "there is a strong linkage between a neutral polymorphism in the Factor V gene and expression of APC-resistance." The specification does

not identify the "neutral polymorphism," nor does the specification provide any mutations within the Factor V gene. The specification merely postulates that these exist.

Applicants cite Zbar and Keating *et al.* as teaching that certain DNA polymorphisms are indicative of the presence of a disease gene. Though Zbar and Keating *et al.* suggest that polymorphism can be used in identifying disease genes, these do not remedy the lack of description in the instant specification of diagnostic gene mutations necessary for the practice of the claimed invention. A polymorphism that is associated with a particular phenotype may be linked to a particular "disease gene" that is within the same gene as the polymorphism or that is hundreds of thousands of base pairs away from the linked polymorphism. In the instant specification, not even the linked "neutral polymorphism" is properly described to meet the requirements of USC 112 1st paragraph as applicant does not provide any specific information about the location or structure of this "neutral" polymorphism other than to say that it exists.

Applicant argues that the specification makes clear that the Factor V gene is associated with APC resistance, and that the precise mutation in the Factor V gene is not required for practicing the claimed inventions, as the mutation or mutations would be readily ascertainable. The fact that the Factor V gene may be associated with APC resistance is not sufficient written description to support the claimed methods which require the identification and/or assay of mutations within the gene as no mutations are taught in the specification. A description which renders a claimed invention obvious is not sufficient to satisfy the written description requirement. Applicant further points out that more than one mutation may cause the phenotype, making it difficult, if not impossible to include in the specification every possible mutation in the Factor V gene that may cause APC-resistance. This point underscores the rejection itself; the

structure of the nucleic acid molecules to be detected in the claimed assays are not described or predictable based on the disclosure of the specification. Not a single example within the claimed genus is described in the specification.

Applicant further points out in the third paragraph of page 8 of the response that the precise mutation is not necessary to practice a method for determining an increased risk of developing thrombosis or APC-resistance, citing a quotation from Zbar *et al.* It appears, however, that Zbar *et al.* are teaching that a "genetic marker" is necessary to predict risk with greater precision." In the instant case, no marker has been identified that can be used for the prediction of increased risk, only a suggestion that such a marker exists. Furthermore, most of the claims explicitly recite the detection of a mutation, for example, "the occurrence of a Factor V gene mutation (claim 40)."

Finally, Applicants conclude on page 9 of the response that the specification has provided sufficiently detailed, relevant identifying characteristics as required by case law and the PTO guidelines. However, for the reasons of record, in the rejection and in the arguments presented herein, the examiner does not agree. Accordingly, the rejection is maintained.

A new 112 1st paragraph, lack of enablement rejection is set forth.

New 112 2nd paragraph rejections are set forth.

***Conclusion***

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Juliet C Switzer
Examiner
Art Unit 1634

June 2, 2004